

WHAT IS CLAIMED IS:

- 100200-12462300
1. A method for assaying a candidate compound for its ability to interact with a modified receptor tyrosine kinase (RTK) polypeptide comprising:
    - a) expressing an isolated DNA sequence or variants thereof encoding the modified RTK gene construct wherein said RTK gene contains a synthetic catalytic linker wherein said linker comprises at least one amino acid from the kinase insert domain (KID) of the VEGFR-2 gene catalytic region, in a host capable of producing a form of the polypeptide which form may be assayed for interaction of said polypeptide with said candidate substance;
    - b) exposing said modified polypeptide to said candidate substance; and
    - c) evaluating the interaction of said polypeptide with said candidate substance.
  2. The method of claim 1, wherein said evaluation step further comprises:
    - (a) crystallizing said modified polypeptide in a condition suitable for x-ray crystallography; and
    - (b) conducting said x-ray crystallography on said polypeptide.
  3. A method for assaying a candidate compound for its ability to interact with a modified VEGFR-2 receptor polypeptide comprising:
    - a) expressing an isolated DNA sequence or variants thereof encoding the modified VEGFR-2 gene construct wherein said VEGFR-2 gene contains a synthetic catalytic linker wherein said linker comprises at least one amino acid from the kinase insert domain (KID) of the VEGFR-2 gene catalytic region, in a host capable of producing a form of the polypeptide which form may be assayed for interaction of said polypeptide with said candidate substance;
    - b) exposing said modified polypeptide to said candidate substance; and

c) evaluating the interaction of said modified polypeptide with said candidate substance.

4. The method of claim 2, wherein said evaluation step further comprises:
  - (a) crystallizing said modified polypeptide in a condition suitable for x-ray crystallography; and
  - (b) conducting said x-ray crystallography on said polypeptide.
5. An isolated DNA sequence or variants thereof encoding a modified RTK gene construct wherein said RTK gene contains a synthetic catalytic linker wherein said linker comprises at least one amino acid from the kinase insert domain of the RTK gene catalytic region.
6. An isolated DNA sequence or variants thereof encoding a modified VEGFR-2 gene construct wherein said VEGFR-2 gene contains a synthetic catalytic linker wherein said linker comprises at least one amino acid from the kinase insert domain of the VEGFR-2 gene catalytic region.
7. The isolated oligonucleotide sequence of claim 6 comprising a DNA sequence or variants thereof in SEQ. ID NO. 5.
8. The isolated oligonucleotide sequence of claim 6 comprising a DNA sequence or variants thereof in SEQ. ID NO. 6.
9. A method of assessing compounds which are agonists or antagonists of the activity of the a modified RTK gene polypeptide wherein said modified RTK gene contains a synthetic catalytic linker wherein said linker contains at least one amino acid from the kinase insert domain of the RTK polypeptide catalytic region comprising:

a) crystallizing said modified RTK polypeptide;

b) obtaining crystallography coordinates for said crystallized modified RTK polypeptide;

c) applying said crystallography coordinates for said modified RTK polypeptide to a computer algorithm such that said algorithm will generate a model of said RTK polypeptide suitable for use in designing molecules that will act as agonists or antagonists to said polypeptide; and

d) applying an iterative process whereby various molecular structures are applied to said computer generated model to identify potential agonists or antagonists to said polypeptide.

10. A method of assessing compounds which are agonists or antagonists of the activity of the a modified VEGFR-2 gene polypeptide wherein said modified VEGFR-2 gene contains a synthetic catalytic linker wherein said linker comprises at least one amino acid from the kinase insert domain of the VEGFR-2 polypeptide catalytic region comprising:

a) crystallizing said modified VEGFR-2 polypeptide;

b) obtaining crystallography coordinates for said crystallized modified VEGFR-2 polypeptide;

c) applying said crystallography coordinates for said modified VEGFR-2 polypeptide to a computer algorithm such that said algorithm will generate a model of said VEGFR-2 polypeptide suitable for use in designing molecules that will act as agonists or antagonists to said polypeptide; and

d) applying an iterative process whereby various molecular structures are applied to said computer generated model to identify potential agonists or antagonists to said polypeptide.

11. The method of claim 10, wherein said modified VEGFR-2 polypeptide comprises the VEGFR2Δ50 polypeptide of Seq. ID No. 5.
12. An isolated DNA sequence comprising a DNA sequence or variants thereof encoding the VEGFR-2 gene construct having the x-ray coordinates of Figure 5.
13. A method for preparing proteins or polypeptides of the receptor tyrosine kinase family such that they are suitable for measurement by x-ray crystallography comprising:
- a) identification of the Kinase Insert Domain within the catalytic domain of said proteins;
  - b) deletion of a specific number of amino acid residues from said Kinase Insert Domain such that the modified polypeptide now has a stable conformation such that it may form a crystalline state suitable for being measured by x-ray crystallography; and
  - c) crystallizing said modified polypeptide.
14. A process of drug design for compounds which interact with RTK polypeptides comprising:
- a) deletion of a portion of the KID of the target RTK polypeptide;
  - b) crystallizing said target RTK polypeptide;
  - c) resolving the x-ray crystallography of said target RTK polypeptide;
  - d) applying the data generated from resolving the x-ray crystallography of said target RTK polypeptide to a computer algorithm which will generate a model of said target RTK polypeptide suitable for use in designing molecules that will

act as agonists or antagonists to said polypeptide; and

e) applying an iterative process whereby various molecular structures are applied to said computer generated model to identify potential agonists or antagonists to said target RTK polypeptide.

15. A process of drug design for compounds which interact with modified VEGFR-2 polypeptides comprising:

a) deletion of a portion of the KID of the modified VEGFR-2 polypeptide;

b) crystallizing said modified VEGFR-2 polypeptide;

c) resolving the x-ray crystallography of said modified VEGFR-2 polypeptide;

d) applying the data generated from resolving the x-ray crystallography of said modified VEGFR-2 polypeptide to a computer algorithm which will generate a model of said modified VEGFR-2 polypeptide suitable for use in designing molecules that will act as agonists or antagonists to said polypeptide; and

e) applying an iterative process whereby various molecular structures are applied to said computer generated model to identify potential agonists or antagonists to said modified VEGFR-2 polypeptide.

16. The method of claim 15, wherein said modified VEGFR-2 polypeptide comprises the VEGFR2 $\Delta$ 50 polypeptide of Seq. ID No. 5.

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